

NSLS-II – Status of the Life Sciences Program



Wayne A. Hendrickson
Chief Life Scientist, Photon Sciences Directorate
X6A Scientific Advisory Committee
10 February 2012

NSLS-II Project Scope

Accelerator Systems

- Storage Ring ($\sim 1/2$ mile in circumference)
- Linac and Booster Injection System

Conventional Facilities

- Ring Building and Service Buildings ($\sim 400,000$ gsf)
- 5 Laboratory/Office Buildings (LOBs) for beamline staff & users
 - 2 full & 3 shell (190,000 gsf)
- Reuse of existing NSLS office/lab space for NSLS-II staff

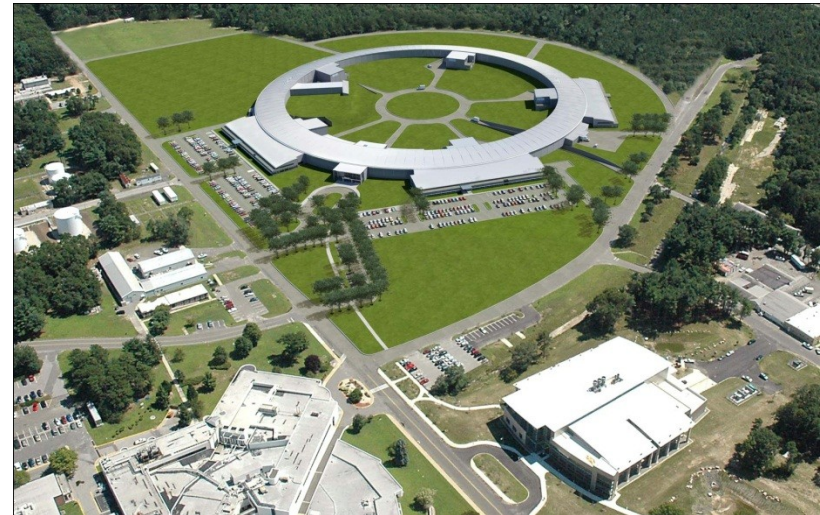
Experimental Facilities

- Initial suite of six insertion device beamlines
- Capable of hosting at least 58 beamlines

Research & Development

- Advanced optics & accelerator components

TPC = \$912M



NSLS-II in Progress

Total Project Cost = \$912M

~ 70% complete by December 2011

Accelerator magnet installations under way

Beneficial occupancy of entire floor in February 2012

Completion expected by March 2014



Key NSLS-II Project Milestones

Aug 2005	CD-0 , Approve Mission Need	(Complete)
Jul 2007	CD-1 , Approve Alternative Selection and Cost Range	(Complete)
Jan 2008	CD-2 , Approve Performance Baseline	(Complete)
Jan 2009	CD-3 , Approve Start of Construction	(Complete)
Feb 2009	Contract Award for Ring Building	(Complete)
Aug 2009	Contract Award for Storage Ring Magnets	(Complete)
May 2010	Contract Award for Booster System	(Complete)
Feb 2011	1 st Pentant Ring Building Beneficial Occupancy	(Complete)
Mar 2011	Start Accelerator Installation	(Complete)
Feb 2012	Beneficial Occupancy of Entire Experimental Floor	
Apr 2012	Start LINAC Commissioning	
Jun 2012	Beneficial Occupancy of 1 st LOB	
Oct 2012	Start Booster Commissioning	
May 2013	Start Storage Ring Commissioning	
Mar 2014	Projected Early Project Completion	
Jun 2015	CD-4 , Approve Start of Operations	

NSLS-II Beamlines Underway

18 Beamline Construction Projects Underway
21 Simultaneous Endstations (SE)
28 Total Endstations (TE)

Beamlines with design
and construction
underway

22 additional beamlines (25 SE) have been
proposed by the user community and approved by
the SAC and NSLS-II but are not yet funded

<u>Beamline Construction Projects</u>	<u>SE</u>	<u>TE</u>
NSLS-II Project Beamlines		
• Inelastic X-ray Scattering (IXS)	1	1
• Hard X-ray Nanoprobe (HXN)	1	1
• Coherent Hard X-ray Scattering (CHX)	1	1
• Coherent Soft X-ray Scat & Pol (CSX)	2	2
• Sub-micron Res X-ray Spec (SRX)	1	1
• X-ray Powder Diffraction (XPD)	1	1
NEXT MIE Beamlines		
• Photoemission-Microscopy Facility (ESM)	2	3
• Full-field X-ray Imaging (FXI)	1	1
• In-Situ & Resonant X-Ray Studies (ISR)	1	2
• Inner Shell Spectroscopy (ISS)	1	1
• Soft Inelastic X-ray Scattering (SIX)	1	1
• Soft Matter Interfaces (SMI)	1	2
ABBIX Beamlines		
• Frontier Macromolecular Cryst (FMX)	1	1
• Automated Macromolecular Cryst (AMX)	1	1
• X-ray Scattering for Biology (LIX)	1	1
Type II Beamlines		
• Spectroscopy Soft and Tender (NIST)	2	6
• Beamline for Materials Measurements (NIST)	1	1
• Microdiffraction Beamline (NYSBC)	1	1
TOTAL		21
		28

Accelerator Operations Ramp Up

FY14	FY15	FY16
1000 Hrs	3500 Hrs	5000 Hrs

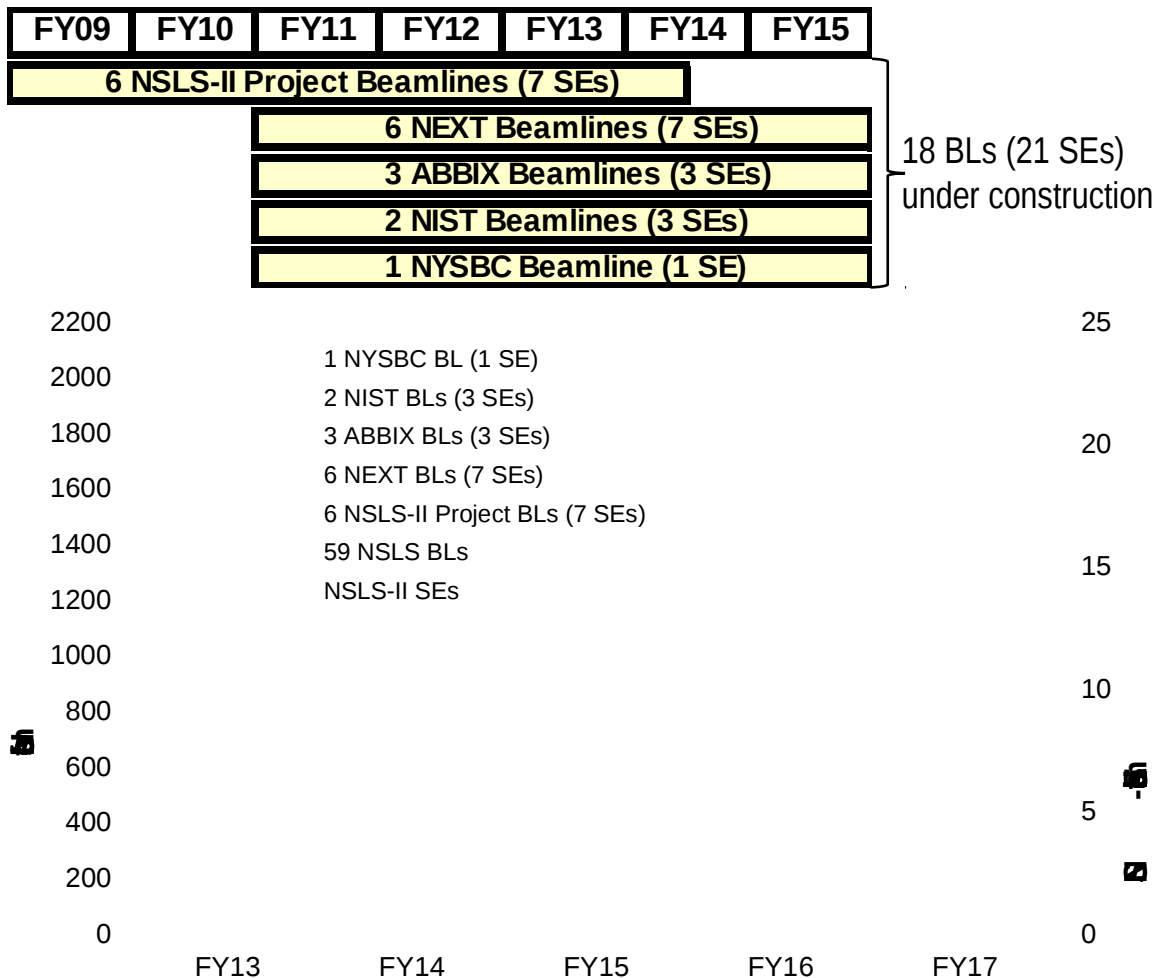
Initial tasks limiting user hours

- Shake-out & conditioning of accelerator
- ID installation
- Beamline commissioning

200 mA	350 mA	500 mA
--------	--------	--------

70 %	85 %	95+ %
------	------	-------

NSLS-II Beamlines and Users



- NSLS stops when NSLS-II starts in mid-FY14
- Rapid ramp up of NSLS-II beamlines for delivering new capabilities and accommodating user community
- Identified transition paths for NSLS beamlines & programs to NSLS-II beamlines
- NSLS-II will host
 - ~ 300 users with 7 SEs in FY 15
 - ~ 600 users with 21 SEs in FY16
 - ~ 1400 users with 21 SEs in FY17 (more if additional beamlines are funded)

SEs = Simultaneous Endstations

Life Sciences Workshop

Date: 15-16 January
2008

Location: Berkner
Hall

Attendees: 72

Organizers: Lisa Miller,
Bob Sweet, Mark
Chance, Vivian
Stojanoff, Marc Allaire,
Lin Yang, Chris
Jacobsen, John
Sutherland



Plans for each research community (MX, SAXS,
XAS, FTIR, STXM, DEI, CD, CDI, MRT)

- Lab space, ancillary facilities discussion
- Breakout sessions (MX, SAXS, Imaging)
- Funding
- Report writing for White Paper

NIH Workshops and Advisory Group

NCRR/NIGMS NSLSII Working Group

Joint study to examine opportunities for
Life Sciences at NSLS-II

Meeting in Bethesda
Working group report

27-28 April 2008
8 August 2008

Workshop on Future Life Sciences Synchrotron Research at NSLS-II

Meeting in Bethesda

4-5 June 2009

NIH Advisory Group for NSLS-II Beamline Development

Initial meeting
NSLS-II presentations

24 May 2010
24 February 2011

Beamline Development Proposals

- **Project Beamlines:**

- Development in progress
- 4 of 6 have biology components (mostly minor)

- **Response to 2010 Call:**

- 54 Beamline Development Proposals received and reviewed by SAC
- 31 Type I approved, 3 Type II approved, 20 Type I not approved
- Funding and designs in progress for some
- 13 of 34 for biology, at least in part

- **Response to 2011 Call:**

- 14 Beamline Development Proposals received
- Reviews by SAC panels in November/December
- 4 of 14 for biology

Macromolecular Crystallography

Acronym	Application	Spokesperson or Beamline Scientist	Source
Approved 2010 Proposals			
FMX	Frontier macromolecular crystallography	Robert Sweet	U
AMX	Automated macromolecular crystallography	Dieter Schneider	U
NYX	NYSBC microdiffraction beamline	Wayne Hendrickson	U
SM3	Correlated spectroscopy and MX	Allen Orville	3PW
2011 Proposals			
HMX	High-energy macromolecular crystallography	Vivian Stojanoff	U
LAX	Low-energy anomalous x-ray diffraction	Wayne Hendrickson	U

U = undulator; 3PW = three-pole wiggler

Frontier Macromolecular Crystallography (FMX)

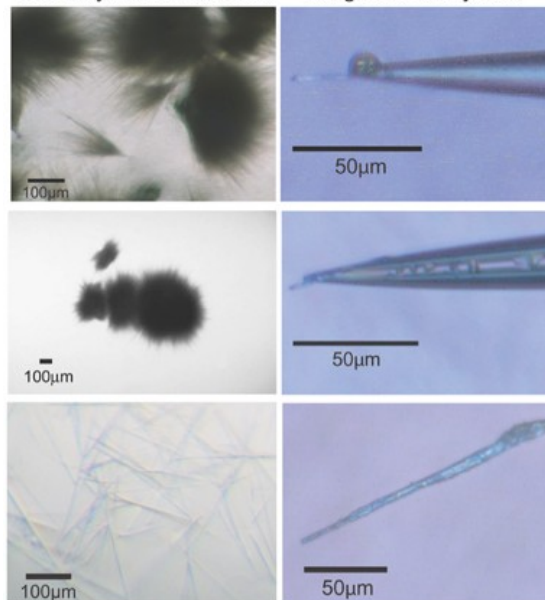
FMX at NSLS-II:

- This MX beamline will exploit the finest properties of NSLS-II and push the state of the art in x-ray optics.
- The tunable, one micron, variable divergence beam handles small crystals, and very large unit cells.
- Preserving beam coherence makes new experiments possible.
- Cryogenic automation at the state of the art provides convenience for users.

Examples of Science Areas & Impact:

- **STRUCTURAL BIOLOGY:** The most interesting structures are often the most difficult. This beamline will push new limits in crystal size.
- **BIOCHEMISTRY:** Knowledge of intermediates in enzymatic pathways expands our understanding of cellular and microbiological processes.
- **PHYSIOLOGY AND MEDICINE:** Knowing how drugs interact with their targets is essential to development of improved and new pharmacologically effective compounds.

Microcrystalline clusters Single microcrystals



Crystals of β amyloid, which are always long and very thin.

From: Sawaya MR, Sambashivan S, Nelson R, Ivanova MI, Sievers SA, Apostol MI, Thompson MJ, Balbirnie M, Wiltzius JJ, McFarlane HT, Madsen AØ, Riekel C, Eisenberg D. Nature 447, 453-7 (2007).

Beamline Capabilities:

TECHNIQUE: Macromolecular Crystallography

SOURCE: Canted U21 In-vacuum Undulator

ENERGY RANGE / RESOLUTION: 5-20 keV; $\Delta E/E \sim 5 \times 10^{-4}$

BEAM SIZE: from 1x1 to 100x100 μm^2 .

Diffraction Resolution to 1 Å

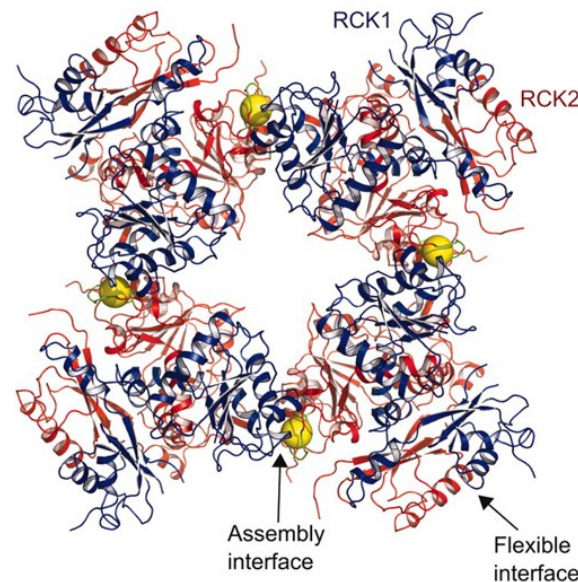
Flexible Access and Highly Automated Beamline for Macromolecular Crystallography (AMX)

AMX at NSLS-II:

- Will provide structural biologists with ready access to an advanced facility for precise structure determinations at unprecedented rates
- Will optimally exploit the unique source characteristics and deliver a very high flux in a suitably small focused beam
- Will be highly automated to support remote access and extensive experimental studies

Examples of Science Areas & Impact:

- **STRUCTURAL BIOLOGY:** Atomic structures of large protein and nucleic acid complexes, including membrane proteins, are prerequisites to gaining insights into their function, interaction, and dynamics, thus creating molecular movies
- **BIOCHEMISTRY:** Structural analysis of all intermediates in entire enzymatic cycles and pathways will expand our understanding of cellular and microbiological processes
- **PHYSIOLOGY AND MEDICINE:** Crystallographic studies of the interactions of drugs with their targets are essential in the development of improved and new pharmacologically effective compounds



Ribbon diagram of the gating ring of the human BK channel Ca-activation apparatus. This channel encodes negative feedback regulation of membrane voltage and Ca-signaling, which plays a central role in numerous physiological processes.

P.Yuan, MD Leonetti, AR Pico, Y Hsiung and Roderick MacKinnon, *Science* 329, 182-6 (2010).

Beamline Capabilities:

TECHNIQUE: Macromolecular Crystallography

SOURCE: Canted U21 In-vacuum Undulator

ENERGY RANGE / RESOLUTION: 5-20 keV; $\Delta E/E \sim 5 \times 10^{-4}$

SPATIAL RESOLUTION: Beam size from 5 to 300 μ
Diffraction Resolution to 1 \AA

NYSBC Microdiffraction Beamline (NYX)

Opportunities for NYSBC Science at NSLS-II:

- Diffraction from micron-sized crystals and rastered scans for optimized diffraction from larger crystals of challenging biological macromolecules and complexes
- Access to a broad range of resonant edges for anomalous diffraction (MAD and SAD) phasing, from U M_V (3.5 keV) to Se K (12.7 keV) to U L_{III} (17.2 keV)
- Optimization of anomalous scattering from high energy resolution for sharp transitions at resonant edges and lower energy for increased f'' with light elements (sulfur)

Example Science Areas and Impact:

- **MEMBRANE PROTEINS:** Challenging structural problems with high relevance in neurobiology & metabolic disorders
- **MACROMOLECULAR COMPLEXES:** Protein-protein interactions in signaling complexes and protein-nucleic acid complexes in transcription or replication
- **METHODS DEVELOPMENT:** Supports efforts for methods to improve phase evaluation and enhance resolution

New York Structural Biology Center (NYSBC) hosts dozens of investigator groups at ten premier institutions



Homolog structure of the SLAC1 anion channel for closing stomata in leaves. Here the trimeric channel protein is shown as viewed from outside the membrane of a guard cell. Each protomer is colored spectrally from the amino-terminus (blue) to carboxy-terminus. Chen et al., *Nature* **467**,1074 (2010).

Beamline Capabilities:

TECHNIQUE: Macromolecular Crystallography

Source: Undulator on a low- β straight section

BEAM CROSS-SECTION: 5 μ - 50 μ

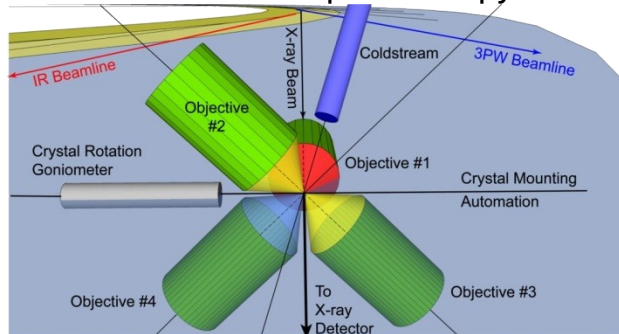
ENERGY RANGE: 3.5 – 17.5 keV

ENERGY RESOLUTION: $\Delta E/E \sim 5 \times 10^{-5}$

Correlated Spectroscopy and MX (SM3)

A unique facility for multi-disciplinary, nearly simultaneous studies of single crystals

- Macromolecular crystallography
- Electronic absorption spectroscopy
- Fluorescence spectroscopy
- Raman spectroscopy
- FTIR spectroscopy
- XAS/XANES/EXAFS spectroscopy



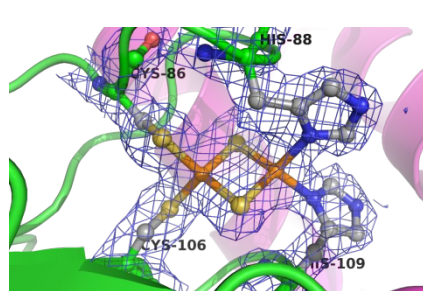
Examples of Science Areas & Impact

Redox state: Define redox states of metalloproteins using structures and spectroscopy from the same sample

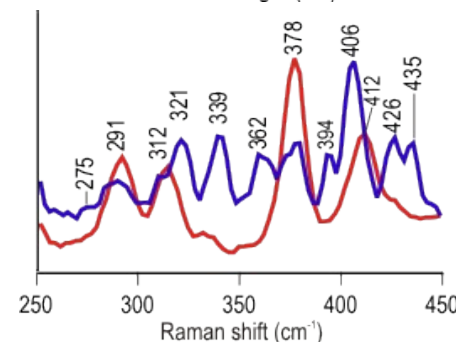
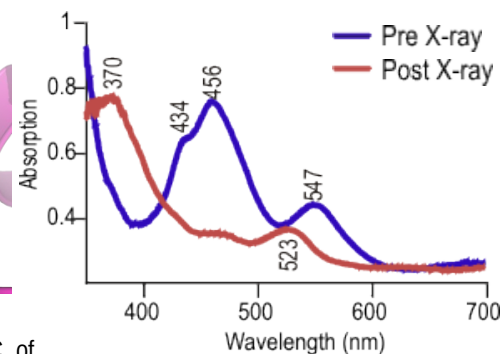
Mystery density: Raman spectroscopy helps assign electron density where ambiguities exist

Photochemistry: Initiate and follow reactions

Mechanisms: Trap and identify reaction intermediates



Correlated studies conducted at X26-C of NSLS have demonstrated the reduction of the iron-sulfur Rieske center in Stachydrine demethylase. The protein structure obtained with MX gives no information on this X-ray induced process. Comparison of the pre and post X-ray exposure absorption (top) and Raman (bottom) spectra, however, do provide clear evidence of this reduction. K. Daughtry, et al., in preparation .



Beamline Capabilities:

Techniques: Macromolecular crystallography, Spectroscopy on- and off-beamline (UV/vis, Fluorescence, IR, Raman, XAS and EXAFS)

Source : Three-pole wiggler

Energy Range: 5-20 keV

Flux: 10^{13} ph/s at 12 keV

Allen Orville



U.S. DEPARTMENT OF
ENERGY

Ultrafast Data Collection on AMX

	X29 at NSLS	X25 at NSLS	AMX at NSLS-II
Beamline Flux	4×10^{11} ph/s	4×10^{11} ph/s	2×10^{13} ph/s
Detector Technology	CCD Composite	Pixel Array	Advanced PAD
Detector	ADSC 315r	Pilatus 6M	Eiger or ADSC DMPAD
Data Set Format	180 frames of 1°	900 frames of 0.2°	900 frames of 0.2°
Exposure Time / Frame	2 s	0.4 s	8 ms
Dead Time / Frame	1 s	2 ms	2 μs
Framing Rate	0.5 Hz	2.5 Hz*	125 Hz
Time / Data Set	540 s = 9 min	360 s = 6 min	7.2 s

*) maximal framing rate = 24 Hz

**Advanced new detectors are required
for full design performance**

Critical parameters:
 μ s dead time,
kHz framing rate

Automounter Requirements

Basic requirements:

- Handle mounted crystals →

in common pucks and	Unipuck, ALS puck (no vials)
less common formats	ESRF basket, Actor puck (in vials)

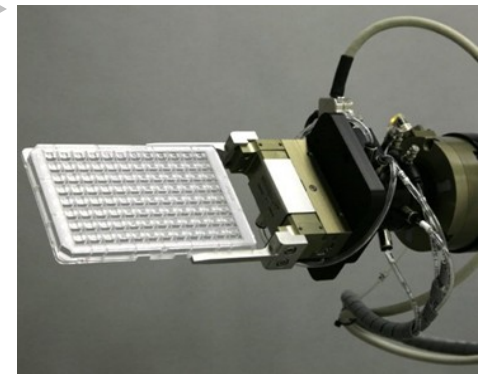


Actor, ALS, and Unipuck

- Handle crystallization well plates →
and similar devices

Maximal specimen processing rates:

Specimen mounting	6 s
Automatic crystal centering	20 s
Data collection within	10 s
Maximal throughput	100 crystals / h
In a 12 hour shift	1200 crystals
	75 pucks in 10 shipping dewars



Greiner 96-well crystallization plate

Biological Scattering

Acronym	Application	Spokesperson or Beamline Scientist	Source
NSLS-II Project Beamlines			
CHX	Coherent hard x-ray scattering	Andrei Flueresu	U
IXS	Inelastic x-ray scattering	Yong Cai	U
Approved 2010 Proposals			
LIX	X-ray scattering for life sciences	Lin Yang	U
ABS	Automated biomolecular solution scattering	Lin Yang	3PW

U = undulator; 3PW = three-pole wiggler

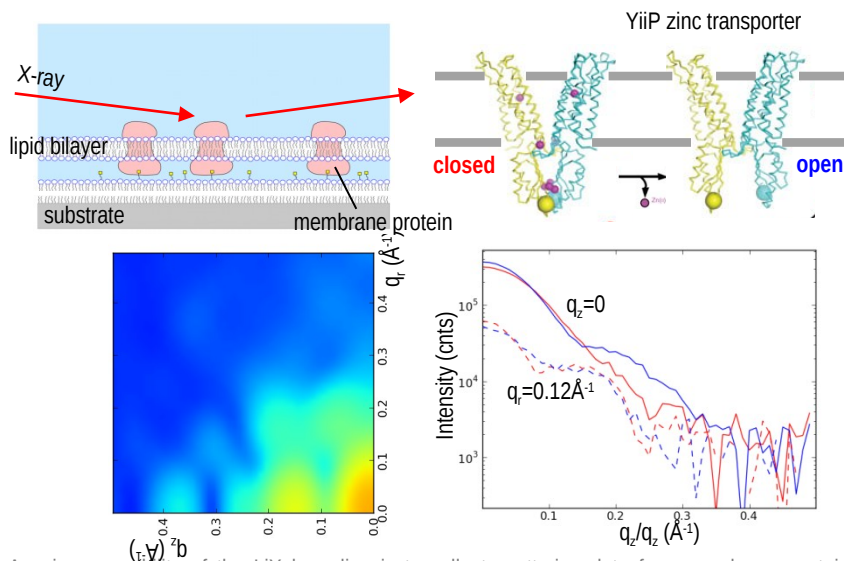
High Brightness X-ray Scattering for Life Sciences (LiX)

LiX at NSLS-II:

- Time-resolved X-ray scattering measurements of proteins and DNA/RNA in solution using flow cells on time scales down to 10 μ s
- Grazing incident scattering from 2D solutions of membrane proteins embedded in near-native membranes
- 1 μ m beam scanning probe imaging and tomography of biological tissues

Examples of Science Areas & Impact:

- **PROTEIN DYNAMICS:** Help understand the dynamic processes of protein conformation change (e.g. folding) and enzymatic reaction
- **MEMBRANE PROTEINS:** Resolve the structure of membrane proteins at low resolution; Reveal how the structures of these proteins change in response to external stimuli
- **TISSUE ENGINEERING:** Help elucidate the relationship between the hierarchical structure in natural and engineered tissues and their functional properties.



A unique capability of the LiX beamline is to collect scattering data from membrane proteins embedded in near native membranes. This is the two-dimensional analogue of the solution scattering technique that has been very successful for soluble proteins in recent years. This figure shows simulated data from YiiP in DOPC bilayer in open and closed states. Simulated noise, based on estimated scattering cross-section, has been added in the line cuts (lower right).

Beamline Capabilities:

TECHNIQUES: Micro-beam, simultaneous small and wide angle X-ray, transmission and grazing incidence

SOURCE: undulator (U23)

ENERGY RANGE / RESOLUTION: 4-20keV @ 0.01%

Q RANGE: 0.002-3.0 \AA^{-1} @ 12keV

Biological Spectroscopy

Acronym	Application	Spokesperson or Beamline Scientist	Source
NSLS-II Project Beamlines			
SRX	Sub-micron resolution x-ray spectroscopy	Juergen Thieme	U
Approved 2010 Proposals			
AIM	Advanced infrared microspectroscopy	Lisa Miller	BM
SM3	Correlated spectroscopy and MX	Allen Orville	3PW
XAS	X-ray absorption spectroscopy	Mark Chance	3PW
XFP	X-ray footprinting	Mark Chance	DW

BM = bending magnet; DW = damping wiggler; U = undulator; 3PW = three-pole wiggler

Biological Imaging

Acronym	Application	Spokesperson or Beamline Scientist	Source
NSLS-II Project Beamlines			
HXN	Hard x-ray nanoprobe	Yong Chu	U
SRX	Sub-micron resolution x-ray spectroscopy	Juergen Thieme	U
Approved 2010 Proposals			
CDI	Coherent x-ray diffraction	Ian Robinson	U
FXI	Long beamline for full-field imaging	Jake Socha	SCW
IRI	Full-field infrared spectroscopic imaging	Lisa Miller	BM
XFM	X-ray fluorescence microprobe	Antonio Lanzirotti	3PW
2011 Proposals			
MIT	Medical imaging and radiation therapy	Avraham Dilmanian	SCW
STX	Scanning transmission x-ray microscope	Juergen Thieme	BM

BM = bending magnet; SCW = superconducting wiggler; U = undulator; 3PW = 3-pole wiggler

ABBIX

Advanced **B**eamlines for **B**iological Investigations with **X**-rays

FMX	Frontier Macromolecular Crystallography (MX)
AMX	Flexible Access and Highly Automated MX
LIX	High Brightness X-ray Scattering for Life Sciences

NEXT: NSLS-II **EX**perimental Tools

ESM	Electron spectromicroscopy
FXI	Full-field x-ray imaging
ISS	Inner shell spectroscopy
ISR	In-situ and resonant hard x-ray studies
SIX	Soft inelastic scattering
SMI	Soft matter interfaces

ABBIX

Advanced **B**eamlines for **B**iological Investigations with **X**-rays



Ab Ex

Abstract Expressionist New York: the Big Picture Museum of Modern Art October 2010



Number 1A, Jackson Pollock (1948)

NIH Support for NSLS-II Beamlines

- **NIH Advisory Committee Definitions**

- Initial suggestions: 2 MX, 1 Scattering, 1 Imaging ID beamlines
- Ultimate endorsement: 2 MX, 1 SAXS/WAXS

- **Relevant Beamline Development Proposal (BDP) Options**

- FMX and AMX for MX
- LIX for scattering
- CDI and FXI for imaging

- **NSLS-II Development of NIH specified BDPs**

- MOU & IAA established in 2010 for ARRA funding of IDs \$12.0M
- MOU established in August 2011 for FMX/AMX/LIX Beamlines
- IAA finalized to transfer NIH FY11 funding 23.4M
- Future NIH funds: FY12 \$5.5M + FY13 \$4.1M = 9.6M
- NSLS-II: Common Beamline Components 3.0M
- **Total** \$48.0M

ABBIX: Biology's Bright Future at NSLS-II



Summer 2009

Design Parameters

- ## Novel design features:

- ## Ultra-low emittance

- ## Pulse Length (rms) ~ 15 psec



X-ray Footprinting (XFP)

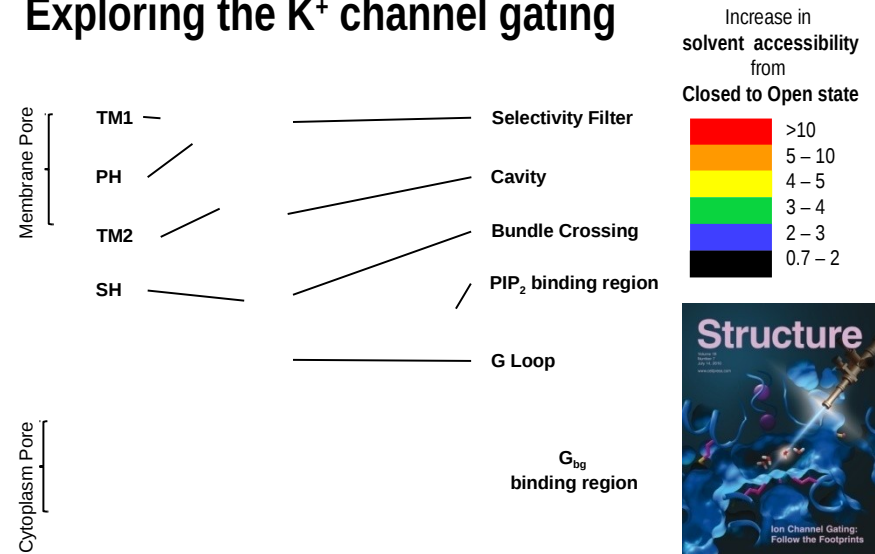
XFP at NSLS-II:

- X-ray mediated hydroxyl-radical footprinting (XFP) will provide a local probe of solvent-accessibility for *in-vivo* and *in-vitro* structural studies of biomolecular complexes and their interactions.
- Time-resolved XFP studies to elucidate local structural dynamics from microsecond to millisecond time scales.
- The high flux density and beam energy range of NSLS-II DW will provide high quality data from microliter volumes of dilute solution samples in near physiological conditions.

Examples of Science Areas & Impact:

- **IN VIVO STUDIES:** Real time ribosomal biogenesis in living cell, cell surface receptor-ligand interactions (drug/protein, antibody/antigen).
- **MEMBRANE PROTEINS:** Understanding of structure and function at molecular level for ion channels, receptors (GPCR), gated pores, H⁺-pumps, transporters, membrane enzymes, dynamics of bound waters in pores, channels and cavities.
- **MEGA DALTON COMPLEXES:** XFP provides structural information for intermediates and activated states of extremely large complexes (e.g. cell cytoskeleton, proteosome assemblies).
- **HYBRID APPROACH:** XFP (local structural measures) along with SAXS (global) is important in deciphering the mechanism of biomolecular assemblies in a "Biology Village" life sciences mode at NSLS-II.

Exploring the K⁺ channel gating



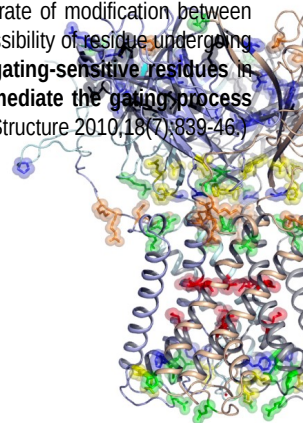
Closed and open states of KirBac3.1 are irradiated with focused 'white beam' of beamline X28C of NSLS. The chemical modification mediated by the hydroxyl radical on the protein side chains are analyzed by high resolution mass spectrometry. The relative rate of modification between these two states are directly correlated to the changes solvent accessibility of residue undergoing modifications. This study has allowed the identification of **novel gating-sensitive residues** in the permeation pathways of the channel and also **residues that mediate the gating process through allosteric conformational rearrangements**. (Gupta et al. Structure 2010,18(7):839-46.)

Beamline Capabilities:

TECHNIQUE(S): Steady state and time-resolved radical mediated Protein and Nucleic Acid

SOURCE: Damping Wiggler

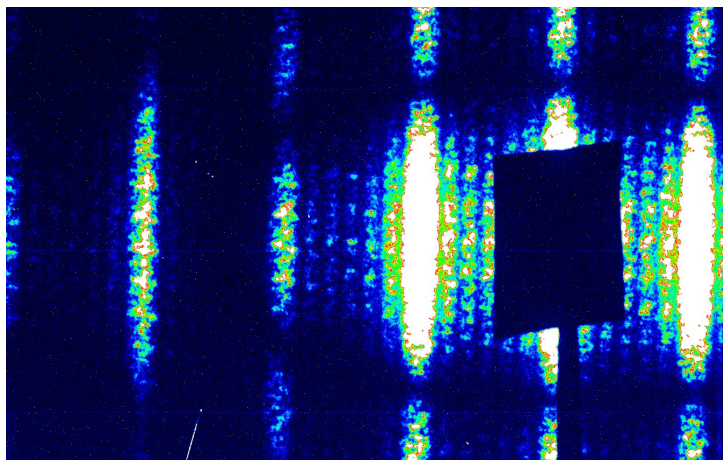
ENERGY RANGE / RESOLUTION: "White"



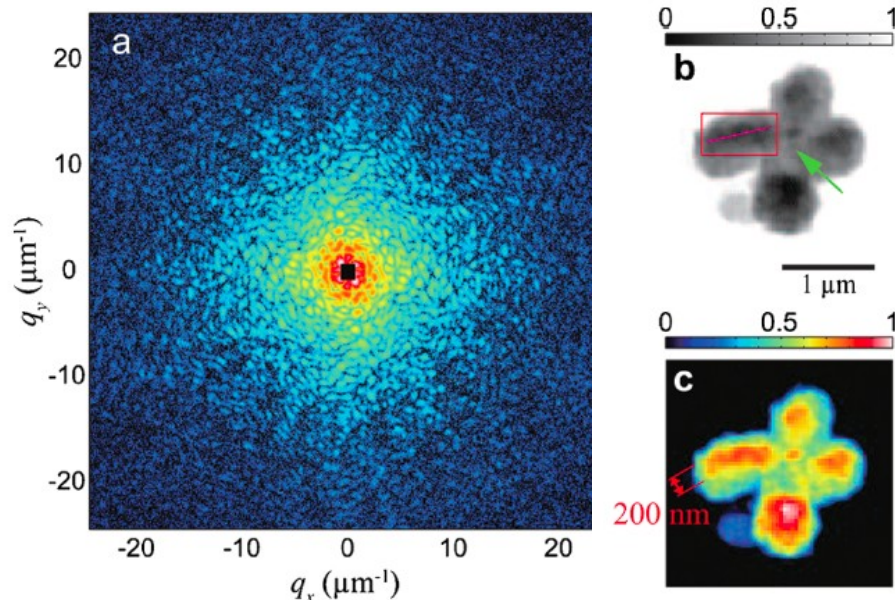
Coherent Diffraction Imaging (CDI)

CDI at NSLS-II:

- Diffraction imaging of crystal shapes in 3D on nm scale
- Diffraction imaging of cryo-frozen cells and tissues
- Imaging of strain fields inside crystals
- Time evolution of shape/strain under working conditions
- Manipulation/deformation/indentation on the nm scale
- Ptychographic imaging for domains in materials
- Ptychographic imaging of biological samples using phase contrast, dark-field and phase encoding methods
- Applications in nanoscale semiconductor devices, strain engineering, catalysis and energy materials



Collagen Phase-plate diffraction,
Felisa. Berenguer and Richard Bean



CDI imaging of a human chromosome, Y. Nishino et al PRL 102, 018101 (2009)

CDI Beamline Capabilities:

IUV20 undulators low- β

Both in-line and Bragg CDI

Long hutch, stable floor

Monochromatic beam 2.5-20 keV (in-line CDI)

Cryo sample manipulation in vacuum

KB optics and ultra precise goniometer



U.S. DEPARTMENT OF
ENERGY

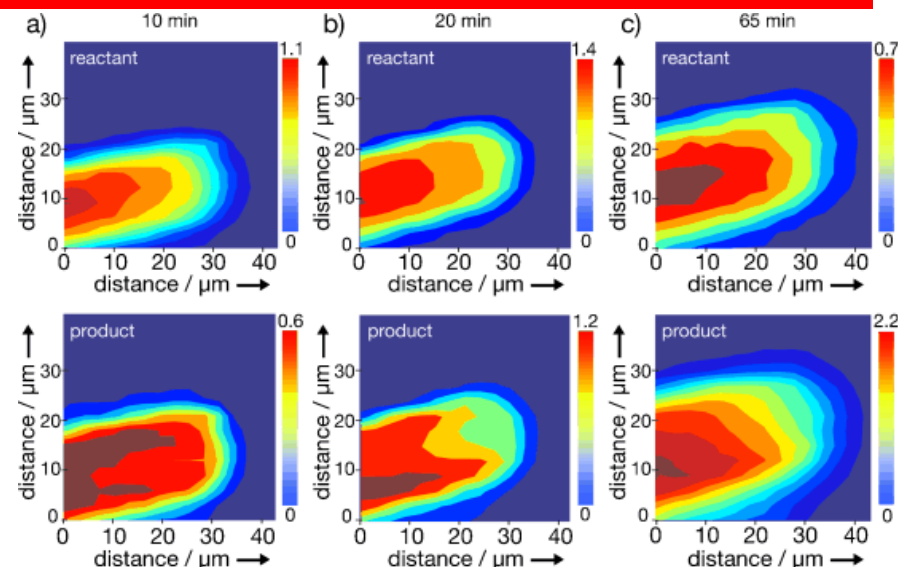
Full-Field Infrared Spectroscopic Imaging (IRI)

IRI at NSLS-II:

- Will enable in-situ studies of organic composition of materials by vibrational spectroscopy
- Measurements from microseconds to days with micromolar detection sensitivity and sub-micron spatial resolution
- The combination of the high brightness and low noise of NSLS-II with a high throughput imaging system will be world leading

Examples of Science Areas & Impact:

- CATALYSIS: In zeolite catalysis, simultaneously image reactants and products in real time for a mechanistic picture of in situ zeolite reaction chemistry
- POLYMERS: In polymer-fiber composites, image the interface morphology under sheer and stretch conditions in situ
- MICROBIOLOGY: In cellulose degradation by bacteria, rapidly image reaction location, rate, and chemical intermediates for improved biofuel production
- MEDICINE: In Lou Gehrig's disease, simultaneously image the formation, structure, and associated cellular toxicity of intracellular superoxide dismutase aggregates



Raster scanned infrared images of a zeolite crystal reacted with 2-chlorothiophene after a) 10, b) 20, and c) 65 min of reaction for the 1412 cm^{-1} reactant band (top) and 1401 cm^{-1} product band (bottom). IRI will enable real-time imaging at much faster time scales without raster-scanning. M. Kox et al., *Angewandte Chemie*, 48, 8990 (2009).

Beamline Capabilities:

TECHNIQUE(S): Fourier transform infrared spectroscopic imaging with a 64×64 focal plane array detector

SOURCE: Dual dipole magnets

ENERGY RANGE / RESOLUTION: $500 - 4000\text{ cm}^{-1} / 1\text{ cm}^{-1}$

SPATIAL RESOLUTION: $\sim 1 - 5\text{ }\mu\text{m}$ full pixel
oversampling and image deconvolution



ENERGY

BROOKHAVEN
NATIONAL LABORATORY
BROOKHAVEN SCIENCE ASSOCIATES